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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/922,227	08/02/2001	Erkki Ruoslahti	P-LJ 4859	7275

7590 04/28/2004

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EXAMINER
PRIEBE, SCOTT DAVID

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 04/28/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

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APPLICATION NUMBER	FILING DATE	FIRST NAMED APPLICANT	ATTORNEY DOCKET NO.
09/422,227			

EXAMINER	
ART UNIT	PAPER NUMBER

DATE MAILED:

INTERVIEW SUMMARY

All participants (applicant, applicant's representative, PTO personnel):

(1) Scott D. Priebe (3) Dr. Erkki Ruoslahti

(2) Cathryn Campbell (4) _____

Date of Interview 4/20/04

Type: ☐ Telephonic ☑ Personal (copy is given to ☐ applicant ☑ applicant's representative).

Exhibit shown or demonstration conducted: ☑ Yes ☐ No If yes, brief description: _____

Agreement ☐ was reached. ☑ was not reached.

Claim(s) discussed: All in general

Identification of prior art discussed: none

Description of the general nature of what was agreed to if an agreement was reached, or any other comments:
Discussed draft R.132 declaration, and the sufficiency of the evidence presented to overcome the enablement rejection. Also, discussed amending claims 8 & 16 to correct new matter.

(A fuller description, if necessary, and a copy of the amendments, if available, which the examiner agreed would render the claims allowable must be attached. Also, where no copy of the amendments which would render the claims allowable is available, a summary thereof must be attached.)

1. ☐ It is not necessary for applicant to provide a separate record of the substance of the interview.

Unless the paragraph above has been checked to indicate to the contrary. A FORMAL WRITTEN RESPONSE TO THE LAST OFFICE ACTION IS NOT WAIVED AND MUST INCLUDE THE SUBSTANCE OF THE INTERVIEW. (See MPEP Section 713.04). If a response to the last Office action has are ready been filed, APPLICANT IS GIVEN ONE MONTH FROM THIS INTERVIEW DATE TO FILE A STATEMENT OF THE SUBSTANCE OF THE INTERVIEW.

2. ☐ Since the Examiner's interview summary above (including any attachments) reflects a complete response to each of the objections, rejections and requirements that may be present in the last Office action, and since the claims are now allowable, this completed form is considered to fulfill the response requirements of the last Office action. Applicant is not relieved from providing a separate record of the interview unless box 1 above is also checked.

Examiner Note: You must sign this form unless it is an attachment to another form.

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Main Facsimile No. 858-597-1585
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Date: April 16, 2004 **Time Sent:**

TO:

Name	Company	Facsimile No.	Contact No.
Examiner Scott Priebe	U.S. Patent and Trademark Office	(571) 273-0733	(571) 272-0733

FROM: Andrea L. Gashler **Direct Phone:** (858) 643-1450

E-Mail: agashler@mwe.com

Sent By: Cris Johnson **Direct Phone:** (858) 643-1427

Client/Matter/Tkpr: 66654-669 (P-LJ 4859) **Original Follow by Mail:** No

Number of Pages, Including Cover: 14

Re: United States Patent Application No.: 09/922,227
Entitled: METHODS OF IDENTIFYING MOLECULES THAT HOME TO A SELECTED ORGAN IN VIVO
Inventors: Ruoslahti and Pasqualini
Filed: August 2, 2001

MESSAGE:

Examiner Priebe:

Attached please find a draft Rule 132 Declaration relating to the above-identified case for your consideration and for discussion with Cathryn Campbell and Dr. Ruoslahti in the interview at 2 p.m. on April 20, 2004.

PATENT
Client-Matter No.: 66654-669
(P-LJ 4859)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of	Confirmation No:
Ruoslahti and Pasqualini	Group Art Unit:
Serial No.: 09/922,227	Examiner: S. Priebe
Filed: August 2, 2001	
For: METHODS OF IDENTIFYING MOLECULES THAT HOME TO A SELECTED ORGAN *IN VIVO*	

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

DECLARATION PURSUANT TO 37 C.F.R. §1.132

Sir:

I, Erkki Ruoslahti, declare as follows:

1) I am the Erkki Ruoslahti who is named as a co-inventor of the above-identified patent application.

2) I understand that the claims of the subject application stand rejected, in part, on the basis that one skilled in the art allegedly would not have been able to identify homing molecules by *in vivo* panning with untagged libraries of molecules at the time the priority application was filed.

3) I believe that in 1995, at the time the priority application for the above-identified application was filed, an ordinary scientist using the teachings of the specification would have been able to use untagged libraries such as peptide and small molecule libraries in the claimed *in vivo* panning methods to recover and identify molecules that selectively home to a selected organ or tissue.

4) Corroboration of identification of homing molecules using an untagged small molecule library in accordance with the teachings of the patent specification is provided herein in paragraphs 5 to 11, which describe identification of homing molecules from a library of 75 random small molecules. The random library was injected into the circulation of mice; selected organs (brain, liver, lung and kidney) were harvested in organic solvent to precipitate proteins, and molecules from the library were subsequently identified in the soluble phase using mass spectrometry.

5) In particular, 75 organic compounds were randomly selected from a 420,000-member library from ChemBridge (San Diego, CA). There was high structural diversity among the 75 organic compounds, and the masses of the compounds differed from each other by at least 4 Da. The library was resuspended in dimethylsulfoxide (DMSO), with each individual compound at a final concentration of 1.33 mM. The 75 ChemBridge compounds and their masses are shown in Table 1.

6) To identify homing molecules, two-month-old female BALB/c mice were anesthetized with avertin. Mice were injected intravenously in the tail-vein with 25 µl of library

(33 nmols per compound). After ten minutes of circulation, the lungs, liver, kidney, and brain were harvested and washed with phosphate-buffered saline (PBS). Each organ was mixed with 5 ml acetone and homogenized with a Handishear hand-held homogenizer (Virtis; Gardener, NY). In some cases, 250 pmol to 2.5 nmol of control compound (ChemBridge 5116670, molar mass of 340 Da) was added as a reference for quantification of the amount of homing compound in target organs. Organ/acetone homogenates were transferred to 15 ml centrifuge tubes and incubated at -80°C for 12 hours for protein precipitation. Following centrifugation at 3,000 x *g* for 30 minutes at 4°C, supernatants were recovered and dried in a SpeedVac. A set of organ extracts prepared from mice injected with 25 µl of DMSO without library compounds served as an internal control for the experiment.

7) Dried organ extracts were resuspended in 100 µl methanol, vortexed for about 10 to 20 minutes and centrifuged in order to pellet debris. Supernatants were recovered, further diluted 1:20 in methanol and 20 µl of the diluted sample analyzed on a Waters® Micromass® LCT mass spectrometer (Milford, MA) at The Scripps Research Institute (La Jolla, CA). Samples were chromatographed in a mobile phase of 90% methanol/9% water and 1% acetonitrile.

8) In order to identify molecules that localized to a particular organ, peaks were identified which were differentially observed in organ extracts from library-injected mice but not in organ extracts from control, DMSO-treated mice. Figures 1A (kidney), 1B (liver), 1C (lung) and 1D (brain) show the results of initial screening experiments in which the

library (upper panel) or DMSO alone (lower panel) was injected into mice. Some extraneous oscillatory signals (patterns of peaks in a regular pattern) were observed in the DMSO samples.

9) The peaks of interest were compared to the known masses of the 75 individual ChemBridge compounds in the library shown in Table 1 to tentatively identify ten molecules which appeared to accumulate in at least one selected organ. Based on HPLC and mass spectrometric results giving an observed spectral peak at about m/z 432 in kidney extracts (Figure 1A), a first homing molecule was identified as compound 5862461, with a known mass of 432.07 g (see Table 1). Similarly, based on an observed spectral peak at about m/z 500 in kidney extracts, a second homing molecule was identified as compound 6074428, with a known mass of 500.01 g. A third homing molecule, with an observed spectral peak at about m/z 298 in liver extract and at about m/z 300 in lung extract, was identified as compound 5343617 with a known mass of 300.08 g. Seven additional molecules were also tentatively identified based on spectral peaks which were differentially present organ extracts from library-injected mice as compared to control mice.

10) When tested individually for their ability to home to selected organs, compounds 5862461 and 6074428 were found to accumulate in the kidney and did not localize to any other tissue (Figures 2A and B, respectively). Furthermore, when injected individually, compound 5343617 localized primarily to the liver and, to a lesser extent, to the lung and kidney as shown in Figure 2C. The spectral patterns of two of these compounds, 5862461 and 5343617, were particularly distinct

because these compounds contain bromine, which exists as two abundant natural isotopes and results in a characteristic two mass unit split in the spectral peak (see Figure 2A, inset). As expected, extracts from organs of control mice injected with DMSO alone did not match the spectral pattern of the homing compounds.

11) Of the other 7 compounds tentatively identified by their spectral peaks, three homed to three of the four selected organs, and the remaining compounds accumulated non-specifically or were not detected when analyzed individually.

12) These results demonstrate that untagged small molecule libraries can be screened by *in vivo* panning and that the homing molecules can be identified using techniques routine in the art at the time the priority application was filed.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements are made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that any such willful false statement may jeopardize the validity of the application or any patent issued thereon.

Date: _____ By: _____
Erkki Ruoslahti

Table 1

ChemBridge Compound number	Mass (g)
5343617	300.08
5135609	304.08
6098554	308.09
7246197	312.07
5904415	316.09
5108221	320.05
6955991	324
7477972	328.1
5225540	332.04
7253800	336.04
5231936	340.09
7383619	344.09
5403771	348.03
5279582	352.12
5377438	356.08
5550053	360
5216419	364.03
5276832	368.12
5155350	372.07
5809106	376
7257635	380.01
5225132	384.02
5380863	388.06
5116670	392.01
5624827	396.04

ChemBridge Compound number	Mass (g)
5578637	404.02
5217141	408.11
5300003	412
5326482	416.04
5246030	420.05
6090295	424.09
7384366	428.06
5862461	432.07
5364112	436.03
7100798	440.07
5569100	444.01
6903967	448.1
6170510	452.01
5169028	456.08
5214985	460.01
5216127	464
5255244	468.02
6873050	472
6987235	476.01
6872990	480
6875321	484.01
5130527	488.05
6987469	492.01
5348584	496
6074428	500.01

ChemBridge Compound number	Mass (g)
7583971	508.01
5768124	512
7567423	516.01
5536652	520.01
5717564	524.01
7497180	528.07
5671388	532
5670039	536.14
5555479	540.06
7575548	544.06
7591015	548.01
5374146	552.02
6394103	556.03
5557349	560.02
5551154	564.06
5711954	568.06
5101382	572.19
5227898	576.56
7609370	580.68
5710134	584.46
5751093	588.52
6968226	592.27
5743815	596.61
5233904	600.53

Figure 1A

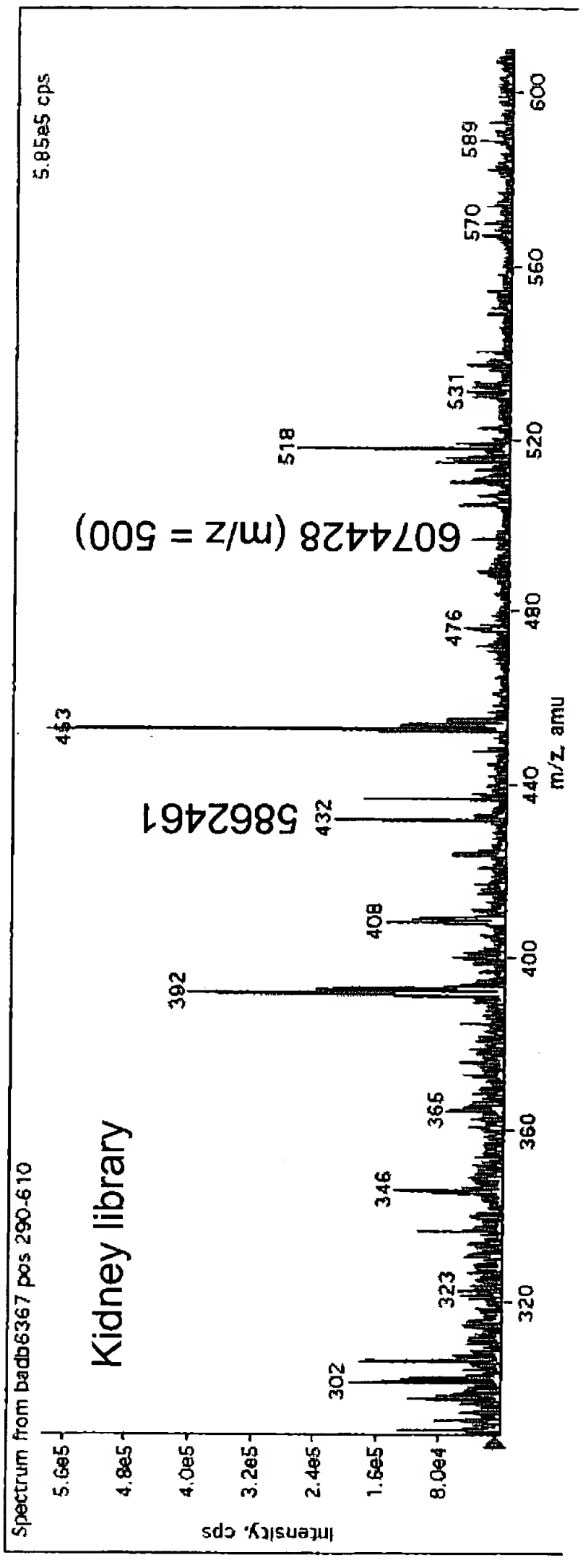

Kidney library
Spectrum from badb6367 pos 290-610
5.85e5 cps
Intensity, cps
m/z, amu
5862461
6074428 (m/z = 500)
Kidney DMSO
Spectrum from badb6368 pos 290-610
4.46e6 cps
Intensity, cps
m/z, amu

Figure 1B

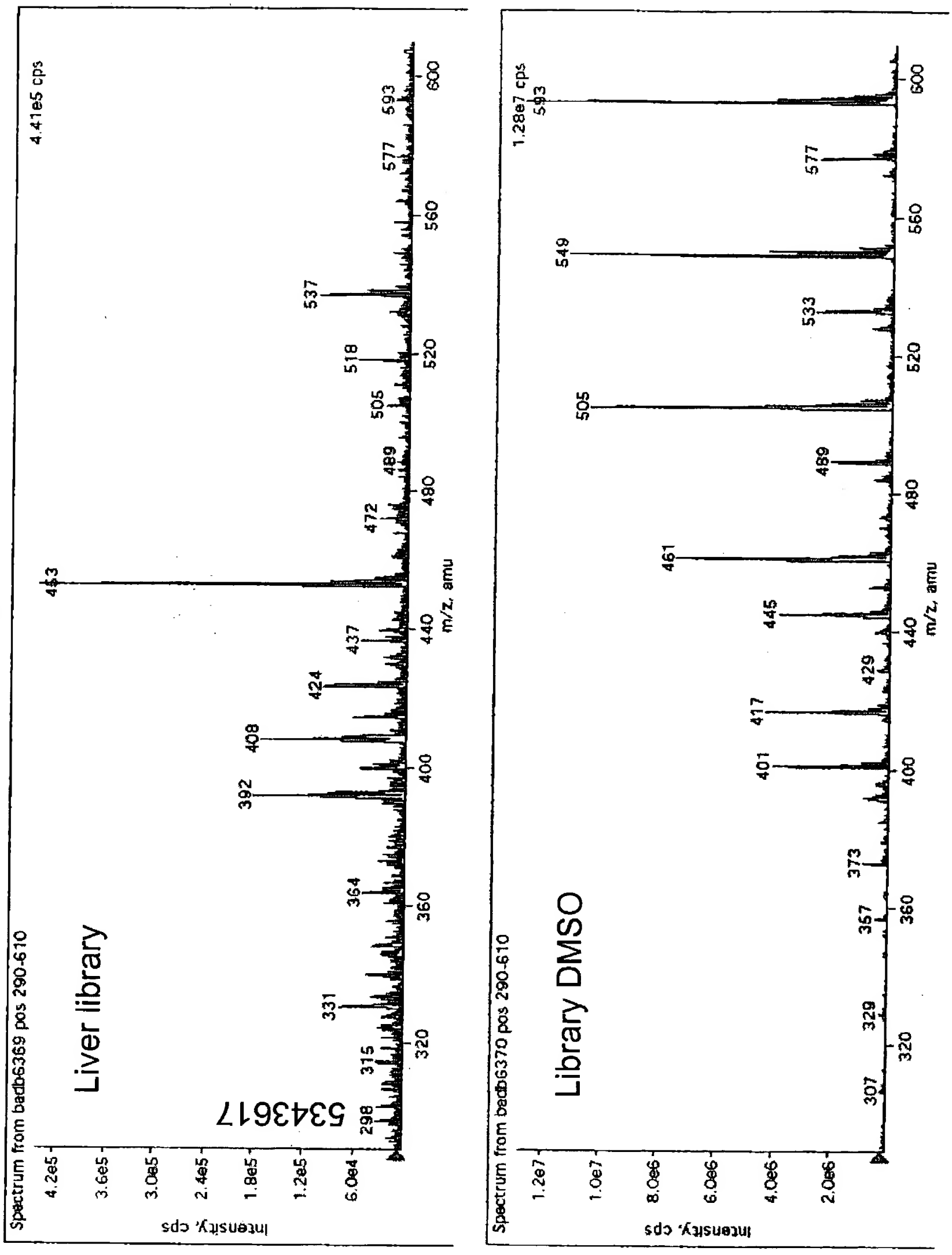

Liver library
5343617
Spectrum from badb6369 pos 290-610
4.41e5 cps
Intensity, cps
m/z, amu
Library DMSO
Spectrum from badb6370 pos 290-610
1.28e7 cps
Intensity, cps
m/z, amu

Figure 1C

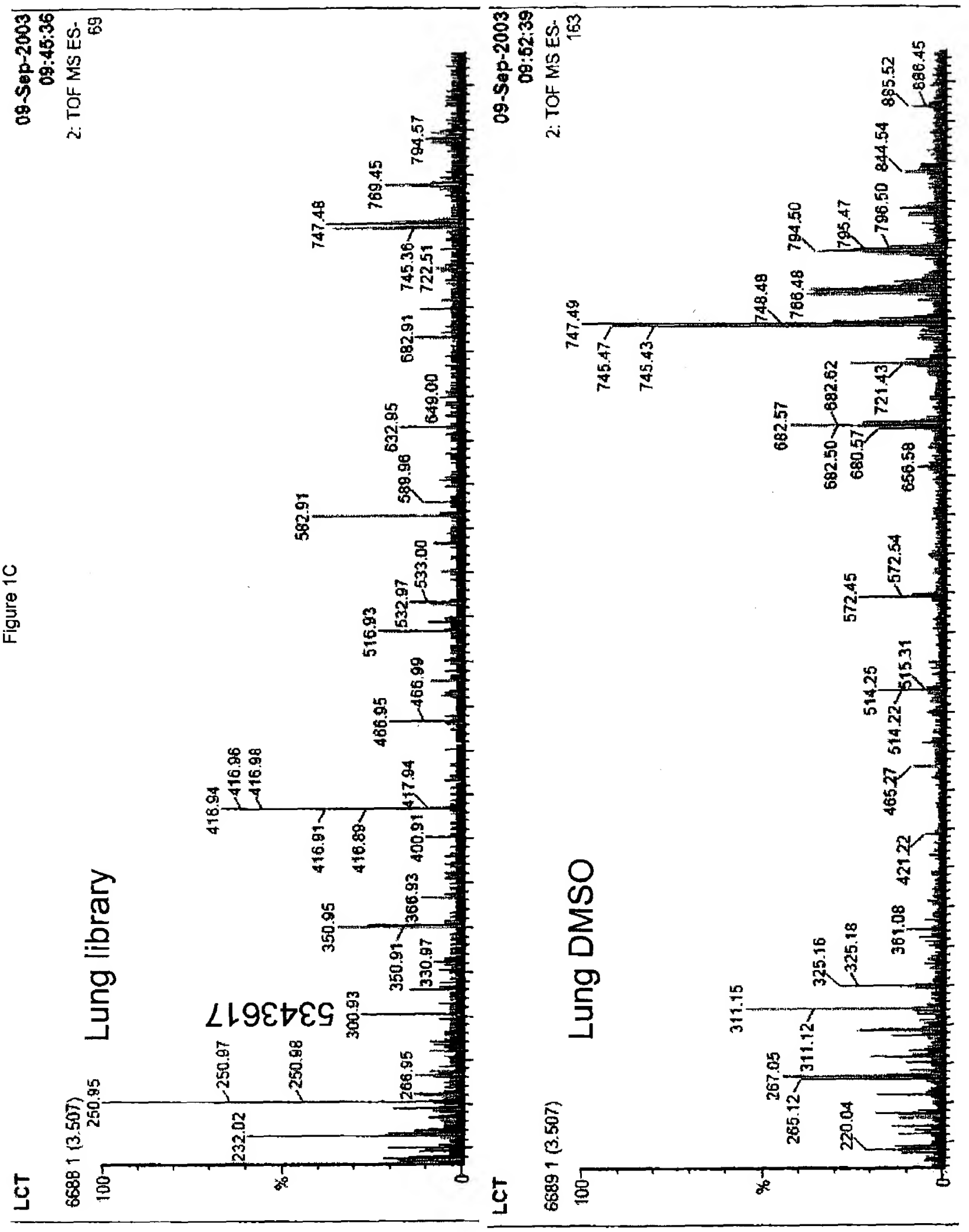
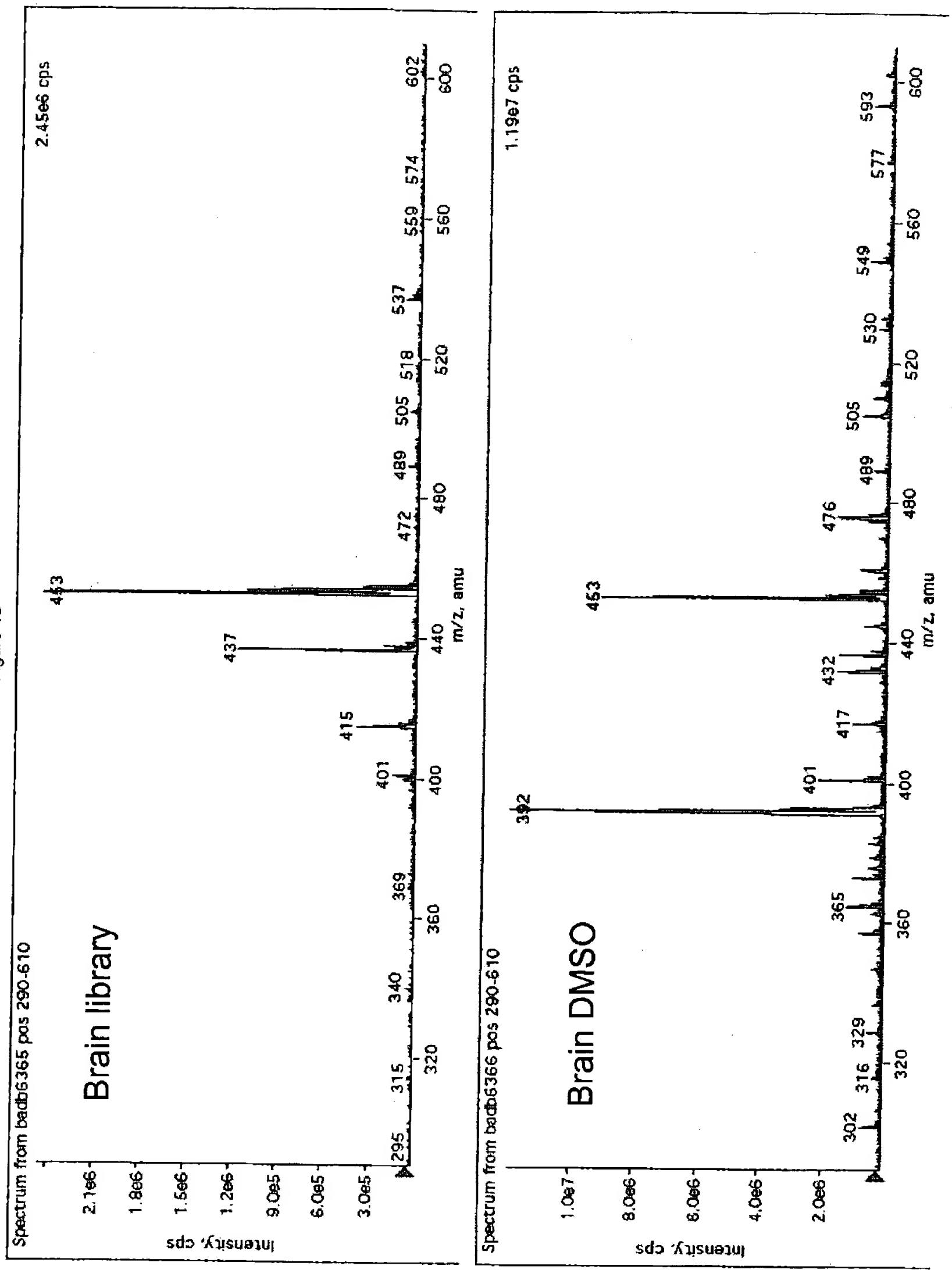

LCT
6688 1 (3.507)
09-Sep-2003
09:45:36
2: TOF MS ES-
69
Lung library
5343617
100
%
0
582.91
589.98
632.95
649.00
682.91
747.48
769.45
794.57
516.93
532.97
533.00
745.36
722.51
416.94
416.96
416.98
416.91
416.89
417.94
400.91
350.95
366.93
350.91
330.97
300.93
486.95
466.99
250.95
250.97
250.98
232.02
266.95
LCT
6689 1 (3.507)
09-Sep-2003
09:52:39
2: TOF MS ES-
163
Lung DMSO
100
%
0
747.49
745.47
745.43
748.48
786.48
794.50
795.47
796.50
844.54
885.52
686.45
682.57
682.62
682.50
680.57
721.43
656.59
572.45
572.54
514.25
514.22
515.31
465.27
421.22
361.08
325.16
325.18
311.15
311.12
267.05
265.12
220.04

Figure 1D


Brain library
Spectrum from badb6365 pos 290-610
Intensity, cps
2.1e6
1.8e6
1.5e6
1.2e6
9.0e5
6.0e5
3.0e5
295
315
320
340
360
369
400
401
415
Brain DMSO
Spectrum from badb6366 pos 290-610
Intensity, cps
1.0e7
8.0e6
6.0e6
4.0e6
2.0e6
302
316
329
360
365
392
400
401
417
2.45e6 cps
453
437
440
472
480
489
505
518
520
537
559
560
574
600
602
1.19e7 cps
453
432
440
476
480
489
505
520
530
549
560
577
593
600
m/z, amu

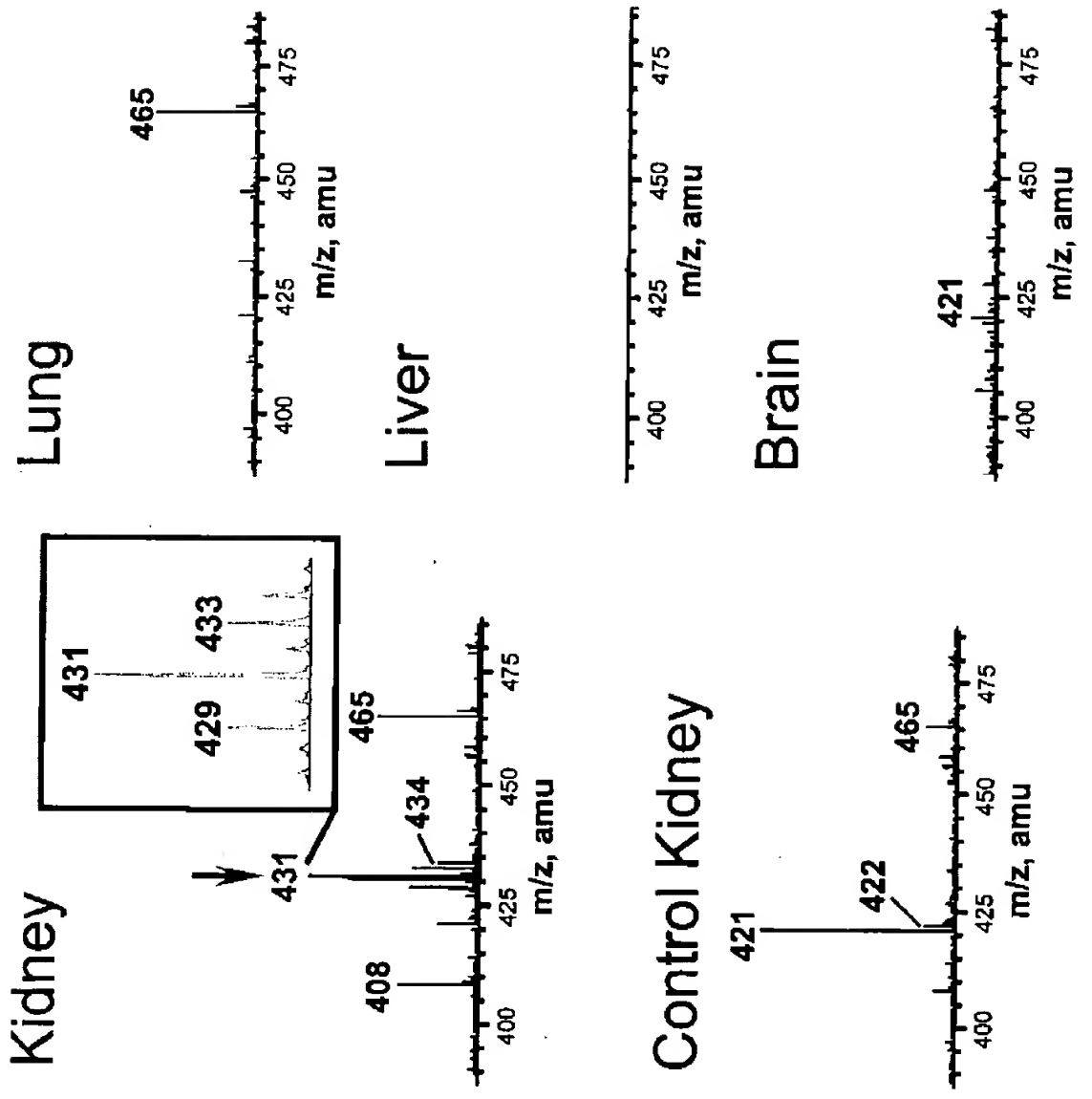

Lung
465
400
425
450
475
m/z, amu
Liver
400
425
450
475
m/z, amu
Brain
421
400
425
450
475
m/z, amu
Kidney
431
433
429
465
434
431
408
400
425
450
475
m/z, amu
Control Kidney
421
422
465
400
425
450
475
m/z, amu

Figure 2A

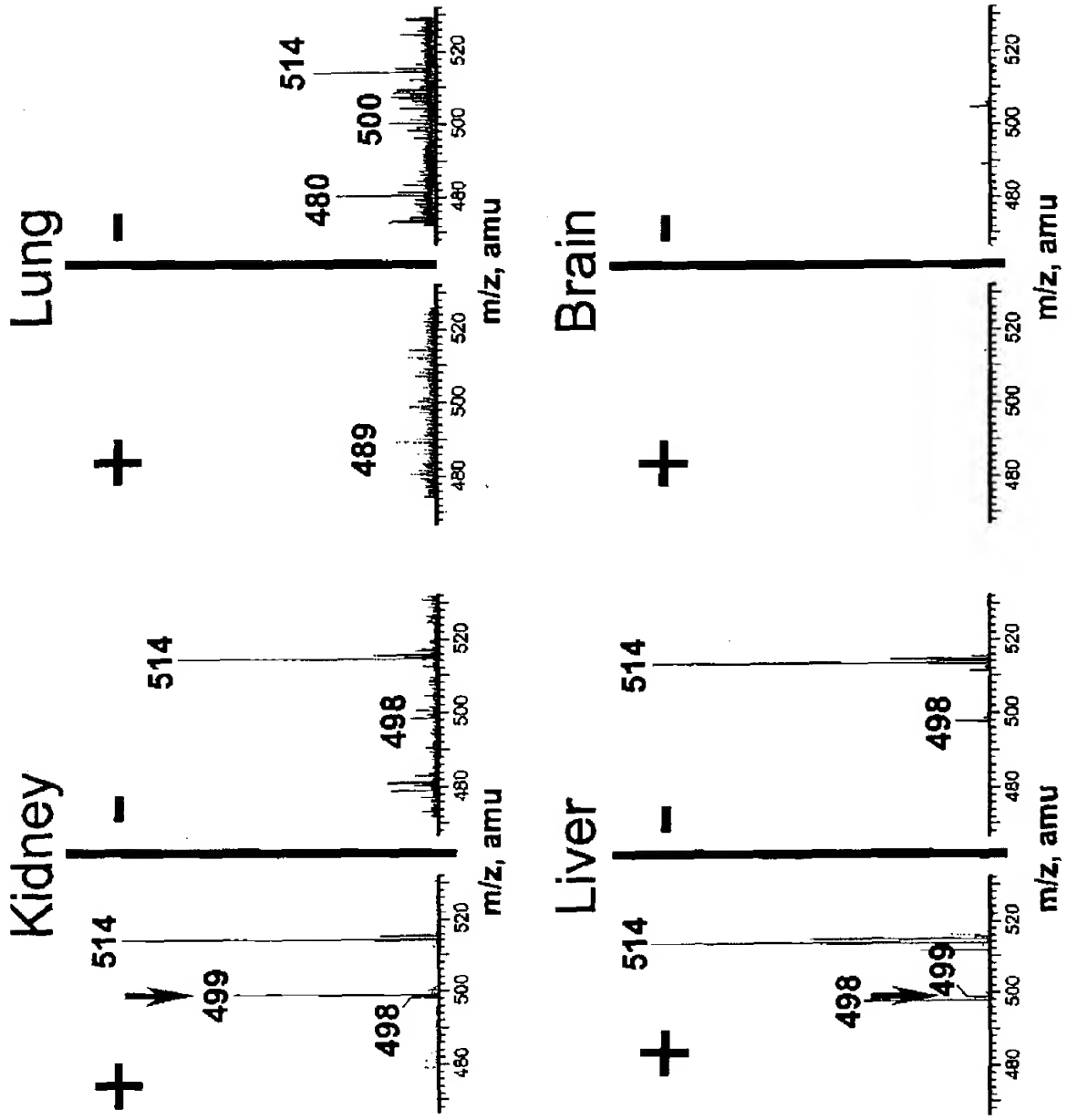

Lung
-
+
514
500
480
489
480
500
520
m/z, amu
Brain
-
+
480
500
520
m/z, amu
Kidney
-
+
514
499
498
514
498
480
500
520
m/z, amu
Liver
-
+
514
498
514
499
498
480
500
520
m/z, amu

Figure 2B

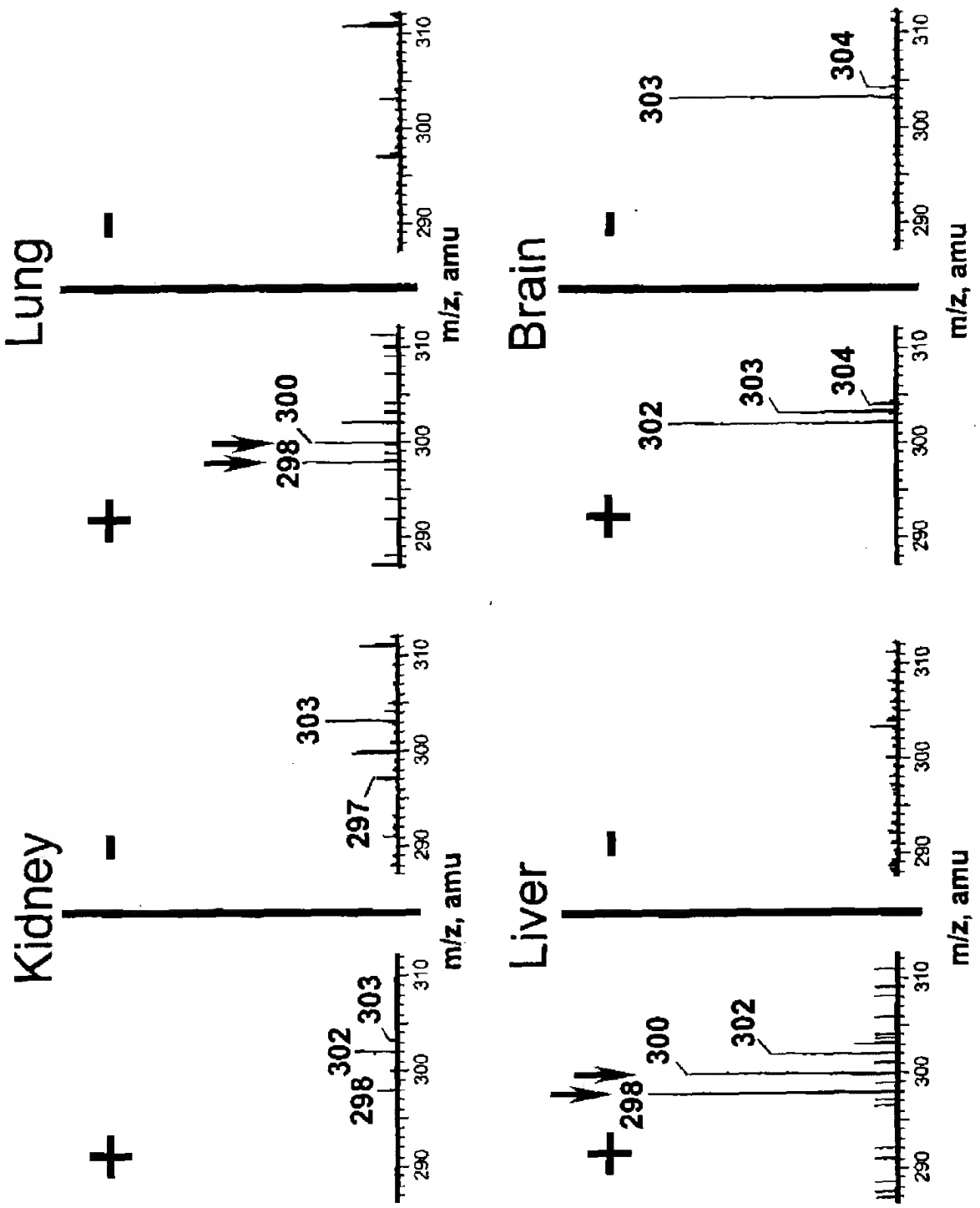

Lung
-
+
298
300
303
304
Brain
302
Kidney
297
Liver
m/z, amu
290
300
310

Figure 2C